

total incidence of leukemia in fostered F mice will probably not exceed 40%, whereas the incidence in unfostered strain F mice is 55%.

Summary. Preliminary breeding experiments did not indicate that a specific "milk-influence" (as for mammary cancer) is con-

cerned in the development of leukemia in strain F mice. The incidence of leukemia in a group of 48 strain F mice fostered by low leukemia-strain mice was, however, somewhat lower than in unfostered controls of the same strain.

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Pathological Studies of Acute Biotin Deficiency in the Rat.*

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Several groups of workers¹⁻⁵ using different types of egg-white rations have reported varying degrees of paralysis in rats. Nielsen and Elvehjem⁵ have shown that this paralysis could be prevented and cured by crystalline biotin. The histopathology of the acute form of this deficiency has been studied and is herewith reported.

Methods. The observations which are described at this time were made on tissues from rats in which an acute biotin deficiency had been produced by Nielsen and Elvehjem⁵ on their basal egg-white ration. Control rats were maintained on the basal ration supplemented with 1 μ g of biotin per day. At the time when the paralysis in the biotin-deficient rats had become extremely severe, the rats were killed and autopsied. Comparable controls were sacrificed at the same time. The thymus, thyroid, liver, adrenal, kidney, testis, epididymis, regions of the denuded skin and leg muscles were fixed in Bouin's fluid and then stained in hematoxylin and eosin. A portion of the spinal cord and 1 sciatic nerve were

fixed in 10% formalin buffered at pH 7.0. This portion of the spinal cord and one half of the sciatic nerve were stained by a modified Marchi osmic acid technic.⁶ The other half of the sciatic nerve was used for the preparation of frozen sections for observation in the polarizing microscope. Another portion of the spinal cord and the other sciatic were fixed in a fluid consisting of 95% ethanol 100 parts, glacial acetic acid 5 parts, and paraldehyde 2 parts. These tissues were stained by Bodian's silver technic.⁷

Results. The distribution of lesions in the tissues studied is shown in Table I. The thymus grossly appeared much smaller in the biotin deficient animals. Histologically it showed signs of early involution and connective and adipose tissue infiltration.

The testes and epididymi of the deficient animals were very small in proportion to the size of the animal. The tubules of the testis were very small and many signs of a degenerative atrophy were present. There were many atypical spermatids and spermatogonial cells which were being sloughed into the lumina of the tubules. Frequently very large multinuclear cells were seen among the desquamated cells in the lumina. The epithelial cells of the tubules of the epididymis were usually rather high and the lumina were filled with the cells sloughed off in the tubules of the testis.

The skin of the biotin-deficient rats ap-

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¹ Boas, M. A., *Biochem. J.*, 1927, **21**, 712.

² Findlay, G. M., and Stern, R. O., *Arch. Dis. Child.*, 1929, **4**, 1.

³ Parsons, H. T., *J. Biol. Chem.*, 1931, **90**, 357.

⁴ Salmon, W. D., and Goodman, J. G., *J. Nutrition*, 1934, **8**, 1.

⁵ Nielsen, E., and Elvehjem, C. A., *J. Biol. Chem.*, 1942, **144**, 405.

⁶ Swank, R. L., and Davenport, H. A., *Stain. Tech.*, 1934, **9**, 11.

⁷ Bodian, D., *Anat. Rec.*, 1936, **65**, 89.

TABLE I.
Number of Rats Which Developed Histopathologic Changes in the Tissues Studied.

Ration	No. of cases	Spinal cord	Sciatic nerve	Thymus	Testis	Epididymis	Skin	Muscle
Basal	20	0	0	12	20	20	20	20
Basal + 1 μ g biotin/day	6	0	0	0	0	0	0	0

peared very dry, in some of the cases rather scaly and in all cases there was a very great loss of hair. There appeared to have been an almost complete sloughing of the stratum corneum so that the cornified layer of the epidermis was present in only small areas of the skin. In all cases the stratum Malphigi was rarely more than two cells thick. The hair follicles were filled with cornified debris.

The muscles of the biotin-deficient rats grossly appeared very small and pale. Histologically it was seen that the fibers were atrophied and only faintly striated. There did not seem to be any complete destruction of the fibers or any connective tissue replacement.

In these rats with severely spastic gait, no myelin degeneration was found in either the spinal cord or the sciatic nerves. The axon cylinders and nerve cells also appeared normal.

The thyroid, liver, adrenal and kidney were all normal.

Discussion. The involution of the thymus would appear to be an early manifestation of the ageing process. The degenerative atrophy of the testis and epididymis do not seem to be specifically characteristic of this deficiency

since very similar conditions have also been seen in riboflavin⁸ and pantothenic acid⁹ deficiency.

The normal condition of the spinal cord and peripheral nerves observed in these rats does not agree with the observations of Findlay and Stern² who reported a diffuse infiltration of small round cells into the gray matter of the spinal cord and slight but definite myelin changes in the peripheral nerves of rats maintained on an egg-white ration. However these investigators used a ration which was quite low in the vitamin B complex and the lesions observed may have been due to the deficiency of one or more of those factors. It may be, however, that in a more chronic biotin deficiency than that studied by us, some pathology of the nervous system would become evident.

Although the spastic paralysis observed in an acute biotin deficiency is grossly similar to that obtained in riboflavin deficiency,⁸ the pathology seems to be different. At present it appears that the paralysis observed in these acutely biotin-deficient rats is not due to a neural lesion.

Summary. The pathology occurring in the thymus, testis, epididymis, skin and muscles of the acutely biotin-deficient rat is reported. No degeneration of the spinal cord or sciatic nerves was observed despite the very extreme spasticity which occurred in many of these acutely deficient animals.

⁸ Shaw, J. H., and Phillips, P. H., *J. Nutrition*, 1941, **22**, 345.

⁹ Shaw, J. H., and Phillips, P. H., unpublished data.